

## 2014 Epilepsy Benchmarks: Progress and Opportunities

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In April 2013, the National Institute of Neurological Disorders and Stroke (NINDS) hosted “Curing the Epilepsies 2013: Pathways Forward,” the third in a series of Curing the Epilepsies conferences held in partnership with epilepsy advocacy and professional organizations to assess progress in epilepsy research and help set a research agenda for future years. As an important outcome, these conferences have led to the development of the Benchmarks for Epilepsy Research, which reflect priorities for research toward clinically meaningful advances in understanding and treating the epilepsies. Following this tradition, and with input received prior to, during, and after the April 2013 conference, NINDS developed 2014 Benchmarks for Epilepsy Research. Table 1 lists the 2014 Benchmarks and the responsible stewards. The 2014 Benchmarks for Epilepsy Research are organized into key research goals in four areas in which significant progress should be likely over the next 5 to 10 years. While advances may arise from many different research directions and may not be predictable, these broad goals are intended to serve as a shared framework for focusing our community’s efforts and benchmarking important advances in the field as they are achieved. Responsibility for achieving goals highlighted by the Benchmarks is shared by all members of the broad epilepsy community.

Several themes emerged during discussions to develop the 2014 Benchmarks. First, the epilepsies are a spectrum of rare and more common disorders that vary in disease course and likely in cause, and this heterogeneity represents both opportunities and challenges for epilepsy research. Distinct forms of epilepsy may ultimately require unique approaches to treatment and prevention. It is also likely, however, that individual epilepsy syndromes with known causes or other well-defined features will serve as gateways for understanding mechanisms with broader relevance to other epilepsies. Either way, the range of both causes and clinical features associated with the epilepsies suggests that knowledge and expertise in many disciplines, including neurology, psychiatry, neurosurgery, immunology, cancer biology, cardiology, cell and molecular biology, pharmacology and others, will be critical. As a second theme, there is growing appreciation of a spectrum of conditions beyond seizures that reduce quality of life for people

with epilepsy, including cognitive impairment, neurodevelopmental and intellectual disabilities; psychiatric and behavioral disorders, stigma and other psychosocial issues, and effects on sleep, skeletal, endocrine, reproductive, and other body systems. These conditions, often called comorbidities of epilepsy, have complex relationships with the underlying causes of epilepsy, ongoing seizures and other pathological network activity, and with the effects of seizure treatments. To better reflect this complexity, the 2014 Benchmarks refer instead to epilepsy-related conditions and consequences, within a revised organization that encourages the integration of these topics into research on the epilepsies as a whole. In addition, the 2014 Benchmarks also reflect recognition of a range of factors specific to certain populations that should be considered in understanding the development and treatment of epilepsy and related conditions and consequences, including issues relevant to children, women, the elderly, and other groups.

While the scope of the Benchmarks broadly encompasses many areas of biomedical research on the epilepsies, NINDS recognizes that important advances will also come from areas not explicitly highlighted, such as fundamental basic research in neuroscience. Moreover, focusing on the Benchmarks and biomedical research alone will not be sufficient to ensure better outcomes and improved quality of life for people with epilepsy. A report from the Institute of Medicine (IOM) recently established recommendations and priorities that address public health aspects of the epilepsies beyond biomedical research, including issues related to surveillance and population research, measures for and access to high-quality care, patient and healthcare provider education, and public awareness (1). Together, the Benchmarks and the IOM report serve as complementary guides for the efforts of diverse stakeholders.

In this issue of *Epilepsy Currents*, the volunteers known as the “stewards” of the Epilepsy Benchmarks summarize research progress made since 2013. The Benchmark Stewards group was first organized in 2001 and since that time has included both established and new investigators who have helped NINDS assess progress in the Benchmark areas, identify key challenges and opportunities, and in some cases initiate workshops, symposia, or other activities to help advance research on Benchmarks’ topics. In 2013, the Epilepsy Benchmarks Stewards became a formal committee of the American Epilepsy Society (AES), which is jointly led by Co-Chairs from the AES and the NINDS. Benchmark Stewards are now selected through the AES Committee nominations process. As part of

**TABLE 1. 2014 NINDS Benchmarks for Epilepsy Research**

<b>Benchmark I: Understand the Causes of the Epilepsies and Epilepsy-Related Neurologic, Psychiatric, and Somatic Conditions</b>		
<i>Co-Chairs: Rochelle Caplan, Heather Mefford</i>		
A. Identify new genes and pathways associated with epilepsies and epilepsy-related conditions.		Ann Poduri
B. Identify new infectious, immune, age-related, environmental, or other causes and risk factors associated with the epilepsies and epilepsy-related conditions.		Bernard Chang
C. Determine whether factors related to age, gender, race/ethnicity, socioeconomic status, and other features of specific populations affect risk and mechanisms of epilepsy and epilepsy-related conditions.		Jack Lin
D. Determine whether the bidirectional relationships that exist between the epilepsies and several co-occurring conditions (e.g., neuropsychiatric or neurodevelopmental disorders) result from the same underlying causal mechanisms, interacting mechanisms, or are a consequence of the first presenting condition.		Madison Berl Andrey Mazarati
<b>Benchmark II: Prevent Epilepsy and Its Progression</b>		
<i>Co-Chairs: Aristeia Galanopoulou, Michael Wong</i>		
A. Understand epileptogenic processes involved in epilepsies with neurodevelopmental origins, including those resulting from genetic or presumed genetic causes.		Elizabeth Powell
B. Understand epileptogenic processes involved in the development of epilepsy following traumatic brain injury, stroke, brain tumor, infections, neurodegeneration, or other insults to the brain.		Avtar Roopra Devin Binder Annamaria Vezzani
C. Identify biomarkers that will aid in identifying, predicting, and monitoring epileptogenesis and disease progression, including markers early after injury/insult that identify those people at risk for epilepsy.		Richard Staba
D. Develop or refine models aligned with the etiologies of human epilepsies to enable improved understanding of epileptogenesis and rigorous preclinical therapy development for epilepsy prevention or disease modification.		Ray Dingledine
E. Identify new targets and develop interventions to prevent or modify epileptogenesis and the progression of epilepsy and epilepsy-related conditions.		Adam Hartman
<b>Benchmark III: Improve Treatment Options for Controlling Seizures and Epilepsy-Related Conditions Without Side Effects</b>		
<i>Co-Chairs: Dennis Dlugos, Greg Worrell</i>		
A. Understand the initiation, propagation, and termination of seizures at the network level in different forms of epilepsy.		Kathryn Davis William Stacey
B. Identify biomarkers for assessing or predicting treatment response, including markers that may identify specific populations that are likely to have good outcomes or develop adverse responses.		Jerzy Szaflarski Andy Kanner
C. Develop or refine models that are aligned with etiologies and clinical features of human epilepsies, especially treatment-resistant forms, to enable improved understanding of ictogenesis and preclinical development to improve seizure control with fewer side effects. Establish the sensitivity and specificity of these models with regard to current therapies.		Ray Dingledine
D. Identify, develop, and improve interventions to detect, predict, prevent, or terminate seizures, including approaches suitable for use in the home and other nonmedical settings.		Sridhar Sunderam
E. Identify, develop, and improve antiseizure therapies that target (either alone, or in combination) novel- or multiple-seizure mechanisms.		Patrice Jackson-Ayotunde Mike Rogawski
F. Develop, improve, and implement interventions for effective self-management, including treatment adherence.		Andy Kanner Tobias Loddenkemper
G. Develop and validate objective patient-centered outcome metrics for clinical studies.		Tobias Loddenkemper Beate Diehl
<b>Benchmark IV: Limit or Prevent Adverse Consequences of Seizures and Their Treatment Across the Life-span</b>		
<i>Co-Chairs: Alica Goldman, Curt LaFrance</i>		
A. Understand and limit adverse impacts of seizures on quality of life, including effects on neurodevelopment, mental health, intellectual abilities, and other neurologic and non-neurologic functions.		Tim Benke Miya Asato
B. Understand and limit adverse impacts of antiseizure treatments (medical, surgical, or other interventions) on quality of life, including effects on neurodevelopment, mental health, intellectual abilities, and other neurologic and non-neurologic functions.		Dan Drane Alison Pack
C. Understand risk factors and mechanisms involved in nonepileptic seizures (NES). Develop effective approaches for earlier and accurate diagnosis and treatment.		Tanvir Syed Robert Doss
D. Identify causes, risk factors, and potential preventive strategies for SUDEP and other epilepsy-related mortality (for example, suicide) in people with epilepsy.		Samden Lhatoo
E. Identify the impact of pharmacologic treatment of the epilepsies on fetal and neonatal development. Develop strategies to control seizures in pregnancy without causing harm to either the mother or child.		Alison Pack



their responsibilities as Benchmark Stewards, these volunteers have assessed the research advances made since 2013 and identified both new opportunities and key issues that appear to be obstacles to further progress. A final assessment and progress report on the 2014 Benchmarks will be conducted in 2019 in preparation for a fourth Curing the Epilepsies Conference in 2020.

As a final note, although Epilepsy Benchmarks is formally a joint effort between AES and NINDS, over the past decade a plethora of national and international research consortia and global planning efforts have appeared, which increasingly emphasize the “research without borders” nature of epilepsy research. These include the EuroEPINOMICS and EpiTarget consortia, the International League Against Epilepsy (ILAE) Global Research Priorities and Advocacy Task Force, the Centers Without Walls projects of NINDS such as Epi4K and the Center for Sudden Unexpected Death in Epilepsy (SUDEP) Research, and others. Going forward, harmonizing efforts across national boundaries should accelerate progress toward the day when epilepsy no longer limits human potential. There should also be opportunities to leverage large-scale funding provided by the U.S. Brain Initiative by partnerships with other national efforts of similar scope such as China’s Brain Database, Japan’s Brain/MINDS project, the European Human Brain Project, and the Australian Brain Project. Epilepsy research, which integrates systems physiology, cell and molecular biology, clinical medicine, and other disciplines, lends itself well to large-scale projects.

A major directional change has appeared in the past 3 to 5 years in epilepsy research, away from the development of

additional drugs that target ligand- and voltage-gated ion channels, and toward exploration of new mechanisms that regulate the function or expression level of those ion channels that control seizure threshold (2). Promising new targets and cellular processes involving different aspects of both innate and acquired immunity, metabolism, neuronal plasticity, and control of blood-brain barrier integrity are emerging. New algorithms for seizure detection and prediction are being developed in an ambulatory setting. The special challenges and experimental designs needed to study disease modification in epilepsy have received increasing attention (3). These advances and others are described in the four accompanying articles. We invite you to read the 2014 Epilepsy Benchmarks and the progress since 2013 summarized in the four following articles, and to consider how your unique research interests and talents may be aligned with the 2014 Benchmarks to accomplish these community-wide goals.

## References

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